Particularly, the language "where appropriate" has been deleted from claims 1 and 12. The term "derivative" has been amended to read --homolog-- in claims 1, 7 and 12. Support for this term is found in the paragraph bridging pages 2 and 3 of the Specification. One of ordinary skill in the art in the chemistry field would understand the meaning and scope of the term "homolog".

In claim 7, "derives from" has been changed to --is derived from-- to make clear that the activity is derived from (a) human factor VIII in its form which occurs in plasma or (b) from a genetically engineered factor VIII:C or (c) from a homolog of (a) or (b). Claim 10 has been amended to delete "customary." The language "pharmaceutically compatible stabilizing or buffering agents" is definite.

Claims 1, 2, 3, 6, 8 and 12 have been rejected under 35 U.S.C. § 102(a) as being anticipated by Myers. Myers is alleged to disclose a large scale adaptation of a recently reported glycine precipitation method for the production of factor VIII:C concentrate. The method is alleged to include adding aluminum hydroxide to a glycine buffer to reduce the level of protein contamination in the final preparation. Furthermore, the resultant product is allegedly virus-inactivated by the incorporation of the organic solvent and detergent (TNBP and T80) technique.

The Examiner then alleges that at the industrial level, the method gave 185 IU of F VIII:C activity per liter of starting

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plasma. This, the Examiner deems to be at least equivalent to Applicant's yield.

Finally, the Examiner states that the starting material for the preparation of the product was obtained from volunteer donors and the final product was a sterile filtered solution that was ultimately lyophilized for storage and considered to be suitable for clinical evaluation. Thus, the Examiner concludes that one would immediately envisage a solution with factor VIII:C activity containing a basic amino acid such as glycine and a nonionic detergent containing a high activity for clinical use in light of Meyer's disclosure. This rejection is respectfully traversed.

Under 35 U.S.C. § 102, anticipation requires that the cited prior art reference identically contain all of the claim elements. In re Donohue, 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985). See also, Atlas Powder Co. v. E.I. duPont deNemours & Co., 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984) and Ralston Purina Co. v. Far-Mar Co., Inc., 227 U.S.P.Q. 177, 179 (Fed. Cir. 1985).

Applicant claims a stable factor VIII:C solution with an activity of at least 1000 IU/mg and which contains a natural or basic amino acid and a detergent or an organic polymer.[1] Myers describes a process to produce a factor VIII concentrate with a specific activity of about 4 IU/mg. See Table 2 on page 145 which shows the specific activities (IU/mg protein) of factor VIII obtained during various parts of the process. The final lyophilized product had a specific activity of 4.1 ± 0.6 IU/mg

[1]Organic polymers such as polyethylene glycol are alternatives to detergents.

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protein. Thus, Myers does not teach or suggest an activity of at least 1000 IU/mg.

Myers employs a "solvent-detergent" process as a method of virus inactivation whereby tri-n-butyl phosphate (TNBP) is used as the solvent and Tween 80 as the detergent. Both of these components are required for virus inactivation. However, contrary to the Examiner's position, the final factor VIII solution described by Myers as being suitable for clinical use contained practically no detergent. After virus inactivation, the detergent Tween 80 was removed to a final content of 15-35 ppm (see page 144, under the heading "S/D Reagent Removal Studies").
One of the goals of Myers was to optimize recovery of factor VIII:C while reducing TNBP and Tween 80 to clinically acceptable levels. Thus, Myers teaches away from a factor VIII:C solution containing a detergent and one of ordinary skill in the art would not have been motivated by Myers to use the detergent as a stabilizer.

To summarize, Myers does not teach or suggest a stabilized solution having a specific factor VIII:C activity of at least 1000 IU/mg, containing an amino acid and a detergent or an organic polymer. It is clear, therefore, that Myers does not teach <u>each</u> and <u>every</u> element of the claimed invention as required under 35 U.S.C. § 102 or teach or suggest the claimed invention as required under 35 U.S.C. § 103. The Examiner is requested to withdraw the § 102 rejection over Myers.

Claims 1, 2, 3, 5, 7, 8, 9, 10 and 12 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Kosow et al.

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Kosow is alleged to teach a solution with factor VIII:C activity containing an amino acid. Kosow is alleged to elute the factor VIII complex containing supernatant from a heparin-coupled chromatographic column, concentrate it by ultrafiltration and add a histidine buffer and a glycine stabilizer to the ultrafiltered factor VIII:C solution to provide histidine at a concentration of about 0.25 M and glycine at a concentration of about 0.28M.

The Examiner then states that the product of Kosow is allegedly used as a pharmaceutical as Kosow discloses that the primary therapeutic use of factor VIII:C has been its intravenous administration to hemophiliac patients to control bleeding. This rejection is respectfully traversed.

Column 1, lines 19-41 of Kosow recognizes the problems of factor VIII:C instability, but Kosow solves the instability problem by isolating the VIII:C-VIII:R complex by ultrafiltration. Because the complex which has been purified (isolated) in this manner is stable, no further proteins are required to stabilize for Factor VIII:C activity. Thus, other than recognizing the prior art treatment of using albumin to stabilize factor VIII:C solutions dissociated from the factor VIII complex (see column 3, lines 42-48), Kosow does not teach or suggest stabilization of factor VIII:C solutions per se. Applicants, on the other hand, do not purify by isolation, and <u>do</u> require stabilization of the Factor VIII:C solution.

Kosow's resulting factor VIII complex has activities between 30-60 U/mg as set forth in column 3, lines 40-41, and in the Examples. These values do not teach or suggest applicants'

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stabilized solution with factor VIII:C activity of 1000 IU/mg or more.

Kosow notes at column 13, line 64, to column 14, line 3, that the specific activity of Factor VIII:C is lower when the $CaCl_2$ concentration is high. In Example 15, an attempt was made to lower the $CaCl_2$ concentration presumably in order to elevate activity. A histidine buffer and glycine stabilizer were added to the complex solution. The resulting factor VIII:C activity was 35 units/mg. The use of the buffer and stabilizer to provide a complex concentrate with less $CaCl_2$ would not have suggested to one of ordinary skill in the art a combination of an amino acid with a detergent or an organic polymer to provide a stable factor VIII:C solution having activities of 1000 IU/mg or more. There is simply no motivation to modify Kosow to add detergent or an organic polymer to arrive at the claimed invention.

In conclusion, Kosow does not teach or suggest a stabilized factor VIII:C solution having a specific factor VIII:C activity of at least 1000 IU/mg, or the combination of a detergent or organic polymer and an amino acid for stabilization of a factor VIII:C solution. It is clear, therefore, that Kosow does not teach each and every element of the claimed invention as required under 35 U.S.C. § 102 or teach or suggest the claimed invention as required under 35 U.S.C. § 103. The Examiner is requested to withdraw this rejection.

Claims 1-12 have been rejected under 35 U.S.C. § 103 as being unpatentable over Myers et al. in view of Mathews and further in view of Rasmussen. Myers is alleged to disclose the large-scale

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preparation of a highly purified solvent-detergent concentrate of factor VIII:C. The Examiner concedes that Myers et al. does not teach a pharmaceutical containing a solution. The Examiner then alleges that Myers does teach that the disclosed concentrate is considered to be suitable for clinical use.

The Examiner then alleges that Mathews discloses a process for purifying a protein that has factor VIII activity by column chromatography. The Examiner then alleges that although the final product is not factor VIII:C, it can be obtained by eliminating the use of calcium ions in the buffer so the non-covalent bonds between the factor VIII and von Willebrand factor (factor C) are not broken.[2/] The Examiner further alleges that the inventors found that exposure of proteins to hydration additives causes the apparent ionic interaction of the protein to increase and the apparent hydrophobic action to decrease. Mathews is alleged to disclose hydration additives including sugars, polyhydric alcohols, amino acids and salts. The Examiner states that Mathew's AHF was purified from human plasma and that anion exchange chromatography was used. A physiologically acceptable detergent (Polysorbate 80) was allegedly used to enhance the desorption of the protein from the column. The Examiner states that since the final product of column chromatography is eluted from the column, the final product is a solution. Finally, the

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[2/] The von Willebrand factor is conventionally designated by R. Mathews discloses at col. 8, lines 14-19 that calcium provides a counter-ion for elution and breaks non-covalent bonds to the von Willebrand factor (factor R). Thus calcium is added to remove factor R and to obtain a factor C product. The calcium would not be eliminated to obtain a factor C product as the Examiner states.

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Examiner concedes that Mathews does not teach the final composition as a pharmaceutical, but the Examiner states that Mathews discloses the primary use of factor VIII is intravenous administration to hemophiliac patients.

The Examiner alleges that Rasmussen teaches a process for the production of factor VIII by precipitation of an aqueous solution of cryoprecipitate from blood plasma using polyethylene glycol (PEG) and a salting-in-agent, such as an amino acid. The amino acids are alleged to include basic amino acid such as lysine, arginine, and histidine as well as polar amino acids such as glutamine and glycine.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention to stabilize factor VIII:C containing solutions with amino acids and one of its salts and/or a detergent or organic polymer. The Examiner states that one would have been motivated to Meyer's preparation of factor:C concentrate using Mathew's process of column chromatography and utilizing the stabilizing agents taught by Rasmussen. This rejection is respectfully traversed.

To prove a prima facie case of obviousness, an Examiner must articulate reasons for making the necessary modifications and substitutions in the prior art which are required to arrive at the claimed invention, and the prior art itself must contain some suggestion or motivation to make these modifications. In re Fine, 5 U.S.P.Q.2d 1596, 1598-1600 (Fed. Cir. 1988). The Examiner has failed to meet this burden.

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As discussed earlier, Myers does not teach or suggest a stabilized solution having a specific factor VIII:C activity of at least 1000 IU/mg as does the claimed invention. Myers also removes detergent from the solution to make the solution suitable for clinical use.

Mathews describes a process for purifying proteins by means of column chromatography in the presence of sugars in concentrations which impel an increase in the yield resolution or the purity of the protein purified in this manner. At column 15, lines 21-38, alternatives to sugars such as polyhydric alcohol, amino acids or salts are listed; however, no amino acids are used in the examples, nor are there any amounts disclosed.

The factor VIII solutions described by Mathews are eluates of column chromatographies. In the final solutions, factor VIII:C is present in 0.1 M tris(hydroxymethyl)aminomethane, pH 7.4, 0.35 M of $CaCl_2$, 1 M sorbitol and 0.1% Tween 80 (Buffer IX, col. 6, lines 58-62 and examples 1-25). No amino acid is present in these examples.

While this solution may be suitable for producing a higher yield or purity of the eluate, nowhere is it taught or suggested that this factor VIII solution is stable under the conditions given or that it can be administered as a pharmaceutical preparation. On the contrary, according to applicants, the solutions of Mathews are unsuited for an I.V. administration, and require further treatment in order to provide a stable, pharmaceutically tolerable factor VIII solution. In fact, the undersigned is informed that the factor VIII solutions described

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by Mathews can be used as a quasi-raw material for the purposes of applicants' invention.

Mathews provides no motivation to one of ordinary skill in the art to modify Myers to arrive at the claimed invention. Particularly, Myers teaches removing any detergent present to provide a clinical solution and therefore, one of ordinary skill in the art would have been motivated to remove any detergent in Mathews to provide a clinical solution.

Rasmussen describes a factor VIII solution to which a "salting-in agent" such as an alkaline amino acid or a carbohydrate is added. These substances are assumed to produce a greater charge difference between the surfaces of the secondary products and the factor VIII molecules so that, during the course of a subsequent PEG precipitation procedure, undesired secondary proteins remain in solution (salting-in) in order to obtain a greater purity of the precipitated factor VIII protein. See column 3, lines 24-34. Therefore, the effect of the added amino acid or sugar is on the secondary proteins and not the factor VIII molecules. See paragraph bridging columns 2 and 3.

Rasmussen does not teach or suggest stabilization of a solution having factor VIII:C activity of at least 1000 IU/mg. The specific activities in Rasmussen obtained are up to 50 units/mg protein. (See Abstract.) Thus, Rasmussen provides no motivation to one of ordinary skill in the art to modify Myers to arrive at the claimed invention.

In summary, Myers in view of Mathews or Rasmussen does not teach or suggest a stabilized solution with factor VIII:C activity

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wherein the activity is at least 1000 IU/mg. Myers' factor VIII clinical preparations do not possess a high activity and do not contain an alkaline or natural amino acid and a detergent or an organic polymer. Mathews' factor VIII column eluates are not suitable as pharmaceutical factor VIII solutions and provide no teaching or suggestion to modify Myers to obtain a stabilized solution as claimed. Finally, Rasmussen employs alkaline amino acids and carbohydrates as salting-in agents for secondary proteins and not as stabilizers for Factor VIII:C and thus there is no motivation to use these agents in Myers as stabilizers. None of the references are directed to a stabilized factor VIII:C solution of very high purity as claimed by applicants. The Examiner is requested to withdraw this rejection.

In view of the foregoing amendments and remarks, Applicant respectfully requests the examination of this application and timely allowance of all pending claims.

If any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Amendment, such extension is hereby respectfully requested. If there are any fees due which are not enclosed herewith, including any fees required from the extension

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of time under 37 C.F.R. § 1.136, the Commissioner is authorized to charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER

By: Susan Wolffe
Susan A. Wolffe
Reg. No. 33,568

Date: September 9, 1993

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FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
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